REMARKS

Claims 1, 5-7, and 19-23 were rejected. Claims 8-18 are cancelled. Thus, claims 1, 5-7, and 19-23 are presently pending. No claim has been allowed.

Formal Matters

The Examiner has stated that references not considered with the IDS received March 14, 2000 because the references were not in Examiner's file. Applicant respectfully submits that

> a copy of any patent, publication, pending U.S. application, or other information listed in an information disclosure statement is not required to be provided if: (1) the information was previously cited by or submitted to, the Office in a prior application, provided that the prior application is properly identified in the IDS and is relied on for an earlier date under 35 U.S.C. § 120 ...

Manual of Patent Examination Procedure § 609 III(A)(2) (8th ed. 2001). Applicants have previously submitted all of the references not considered in the instant application in related applications, and thus are in full compliance with the IDS requirements under § 609 of the *Manual of Patent Examination Procedures*. Nonetheless, Applicants have again enclosed herewith courtesy copies of these references to expedite prosecution.

The Action objected to the name of inventor Rossini appearing without a full first name. A Petition under 37 C.F.R. § 1.182 to correct the above-named inventor to that of Giovanni Rossini is enclosed as well as an unsigned Substitute Declaration and the required fees. A signed declaration will be submitted under separate cover via facsimile.

The Action objected to the title because the title of the invention is allegedly not aptly descriptive. The title has been amended.

The Action also objected to the abstract of the disclosure because it is allegedly not directed to the claimed invention. The abstract has been amended.

In light of the above remarks, Applicants respectfully submit that the objections to the specification have been overcome. Therefore, Applicants request the withdrawal of the objections.

Rejection Under the Judicially Created Doctrine of Nonstatutory Double Patenting

Claims 1, 5-7, and 19-23 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 1-6 of the copending Application Serial No. 09/113,947 (now U.S. Patent 6,462,019).

Applicants have submitted a terminal disclaimer, therefore Applicants respectfully request the withdrawal of this rejection.

Rejection Under 35 U.S.C. § 103(a)

Applicants gratefully acknowledge that Claim 21 is properly viewed as in compliance with 35 U.S.C. § 103(a). Claims 1, 5-7, 19, 20, 22, and 23 are rejected under 35 U.S.C. § 103(a) as being unpatentable over each of O'Keefe, Robin, Murray, and Woo. According to the Action, O'Keefe teaches pentoxifylline for inhibiting bone resorption and Robin teaches pentoxifylline as an anti-osteoporotic agent. The Action also asserts that Murray teaches lactacystin and MG-132, a peptidyl aldehyde, as anti-proliferative in osteoblastic cells and that proteasome activities relate to osteoblastic function. According to the Action, Woo teaches that a peptidyl aldehyde inhibits bone resorption. Applicants respectfully traverse this rejection.

1. The teaching of the inhibition of bone resorption does not make increased bone formation obvious.

Bone resorption and bone formation are distinct processes. Discrete cellular effectors mediate resorption (osteoclasts) and formation (osteoblasts) at different points during the cycle of bone remodeling. While bone remodeling does consist of the coupled processes of resorption and formation, the processes themselves are distinct and non-overlapping. Moreover, it is known in the art that antiresorptive agents affect only the resorptive aspect of the cycle, and therefore ultimately do not increase the rate of bone formation. In fact, bone formation is usually decreased following treatment with antiresorptive agents. *See* Exhibit B at page 1540 ("Since bone remodeling is a coupled process, antiresorptive drugs ultimately decrease the rate of bone

formation."). Therefore, a compound that inhibits bone resorption does not make stimulation of bone formation through osteoblast proliferation obvious.

The O'Keefe and Robin references discuss compounds as antiresorptive agents, and thus teach away from the use of pentoxifylline as stimulators of bone formation. O'Keefe teaches the use of pentoxifylline as an antiresorptive agent. Robin teaches pentoxifylline increases the uptake of calcium, a recognized antiresorptive agent. *See* Exhibit B at page 1540. In light of the fact that bone formation is usually decreased following treatment with antiresorptive agents, these references do not make the use of the cited compounds to induce bone formation through osteoblast proliferation obvious.

Woo does not teach a peptidyl aldehyde as an inhibitor of the claimed invention, and therefore does not make the claimed invention obvious. Woo teaches the use of N-(benzyloxycarbonyl)-L-phenylalanyl-L-tyrosinal as an antiresorptive agent *in vitro* and *in vivo* through the inhibition of collagen hydrolysis or, alternately stated, through inhibiting collagenase activity. *See* Woo, page 135, last paragraph. The instant invention claims the use of peptidyl aldehydes that inhibit proteasomal activity. The proteasome is a large cellular structure with three different, specific protease activities. The proteasome inhibitors available do not inhibit other proteases, but are selective inhibitors of proteasomes. Thus, the teaching of Woo as to a peptidyl aldehyde that inhibits a protease activity would not render a distinct peptidyl aldehyde that inhibits proteasomal activity obvious.

2. Murray is not a proper reference under 35 U.S.C. § 103(a).

The instant invention claims priority as a continuation-in-part to U.S. Application Serial No. 09/361,775, filed July 27, 1999 which is a continuation-in-part of U.S. Application Serial No. 09/113,647, filed July 10, 1998 (now U.S. Patent 6,462,019). MG-132, the compound disclosed in Murray, has a priority claim to the July 10, 1998 filing date of U.S. Patent 6,462,019. MG-132 is disclosed as a proteasomal inhibitor that stimulates bone growth in Example 2 (*e.g.*, column 17, lines 50-54) and Figure 1A. Also, the use of MG-132 to stimulate bone formation is specifically claimed in the original claim set of this application. *See, e.g.,*

claims 3, 6, 9, and 14. Because the Murray reference has a publication date of August 1998, it post-dates the priority date of the claimed invention, and therefore it is not a proper reference under any subsection of 35 U.S.C. § 102. *See* Exhibit D. As a result, claim 19 is free from prior art.

In light of the above arguments, Applicants respectfully submit that the rejection of claims 1, 5-7, 19, 20, 22, and 23 under 35 U.S.C. § 103(a) has been overcome. Therefore, Applicant request the withdrawal of this rejection.

Rejection Under 35 U.S.C. § 112, First Paragraph - Written Description

Claims 5 and 22 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter not described in the specification in such a way to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. According to the Office, the specification contains no "written description of treating any of the disorders in any vertebrates including humans." Applicants respectfully traverse this rejection.

Applicants respectfully submit that written description for treatment of the claimed disorders in any vertebrate including humans is fully disclosed in the specification as filed. The invention is contemplated as being useful for treating any vertebrate including humans as evidenced at page 9, lines 23-24, where the subject for treatment is defined as embracing "human as well as other animal species, such as, for example, canine, feline, bovine, porcine, rodent, and the like." The disorders contemplated as within the scope of the claimed invention are disclosed in detail at page 10, line 1 to page 11, line 2.

In light of the above arguments, Applicants respectfully submit that the rejection of claims 5 and 22 under 35 U.S.C. § 112, first paragraph has been overcome. Therefore, Applicants request the withdrawal of this rejection.

Rejection Under 35 U.S.C. § 112, First Paragraph - Enablement

Applicants gratefully acknowledge that claims 20 and 21 are properly viewed as in compliance with the requirements of 35 U.S.C. § 112, first paragraph. Claims 5 and 22 are rejected under 35 U.S.C. § 112, first paragraph because many of the disorders "are notably difficult to treat effectively." Claims 1, 5-7, 19, 22, and 23 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to reasonably provide enablement for a peptidyl aldehyde. Applicants respectfully traverse this rejection.

1. The instant disclosure provides enabling disclosure for the claimed disorders.

Mere assertion that some of the disorders are difficult to treat does not provide evidence or explanation why the presently claimed invention is not enabling. *See* MPEP 2164.05 ("The examiner should never make the determination based on personal opinion. The determination should always be on the weight of all of the evidence."(emphasis included)). Applicants respectfully request that if the Examiner's rejection is based on facts within his personal knowledge, the Examiner will support this rejection with those facts in an affidavit by the Examiner according to MPEP § 2144.03. According to MPEP § 2144.03,

> When a rejection is based on facts within the personal knowledge of the examiner, the data should be stated as specifically as possible, and the facts must be supported, when called for by the applicant, by an affidavit from the examiner.

Applicants respectfully submit that title 35 does not require that human testing occur within the confines of the PTO proceedings nor is the approval of human protocols by agencies such as the FDA required. MPEP § 2164.05. A disclosure provides adequate guidance to a skilled person in the art if a working example in the form of an *in vitro* or *in vivo* models recognized in the art is provided. *In re Brana,* 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995). "[I]f the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating unless the examiner has evidence that the model does not correlate." MPEP § 2164.02. Neither a rigorous nor an invariable exact correlation is required of an *in vivo* animal model example. *Cross v. Izuka,* 224 U.S.P.Q.2d 739, 747 (Fed. Cir. 1985).

In other words, Applicants do not have to provide actual evidence of success in treating humans. The *in vitro* and *in vivo* assays disclosed in the specification and employed in Dr. Mundy's declaration demonstrate statistically significant enhancement of bone formation using a standard animal model, and thus, under the standards set by the Federal Circuit and the PTO, the instant claims have been enabled.

2. An invention is fully enabled if only routine experimentation is required to practice the invention.

The test of enablement is whether one skilled in the art can make and use the claimed invention from the disclosure in the specification coupled with the information known in the art without undue experimentation, not without any experimentation. *United States v. Telectronics, Inc.*, 8 U.S.P.Q.2d 1217 (Fed. Cir. 1988). A considerable amount of experimentation is permitted if the experimentation is routine. "Routine experimentation does not constitute undue experimentation." *Johns Hopkins Univ. v. Cellpro, Inc.*, 47 U.S.P.Q.2d 1705, 1719 (Fed. Cir. 1998). More specifically, if a compound must retain a certain biological activity to be within the scope of the claimed invention, and one of skill in the art is clearly enabled to perform assays to determine biological activity using routine experimentation disclosed in the specification, the disclosure is fully enabling. *Ex Parte Mark*, 12 U.S.P.Q.2d 1904 (Bd. Pat. App. & Int. 1989) (holding that method claims to produce biologically active muteins by modifying biologically-nonessential cysteines was fully enabled because any mutein within the scope of the claims must have retained its biological activity and the experimentation required to determine biological activity for any given mutein was routine for one of ordinary skill in the art).

3. Routine, not undue experimentation is required for the use of a peptidyl aldehyde in the claimed invention, thus its use is fully enabled.

The claimed invention requires the use of conventional and well-known assays to identify peptidyl aldehydes with the biological activity of the claimed invention. First, the instant specification discloses and exemplifies assays to assess proteasomal activity at page 18, lines 10-23 and in Examples 4 and 5, including commercial sources for the necessary assay reagents.

These assays are both conventional and well known in the art. Second, the instant specification discloses and exemplifies *in vitro* assays to assess the effects of compounds on bone growth at page 21, line 19 to page 22, line 20 and Example 7. These *in vitro* assays require the use of the conventional and well-known procedure of fixing and embedding tissue (*i.e.*, bone) in paraffin wax for histomorphometric assessment. Third, the instant specification discloses and exemplifies *in vivo* assays to assess the effects of compounds on bone growth at page 22, line 21 to page 25, line 23 and Examples 3 and 4. As with the *in vitro* assays, these *in vivo* assays require the use of the conventional and well-known procedure of fixing and embedding tissue (*i.e.*, bone) in paraffin wax for histomorphometric assessment. Fourth, Dr. Mundy's declaration provides evidence that the claimed invention works using the guidance in the specification as filed and what was well-known in the art. *See* Exhibit C. More specifically, Dr. Mundy's declaration demonstrates that (1) the disclosed exemplary compounds function as predicted and (2) the successful use of PSI-epoxide, an undisclosed compound identified by the claimed method in enhancing bone formation. Because the peptidyl aldehyde must have the claimed biological activity (*i.e.*, induce bone formation) to be within the scope of the instant invention, and one of skill in the art is clearly enabled to perform assays to determine biological activity using routine experimentation and the guidance disclosed in the specification, the disclosure is fully enabling.

In light of the above arguments, Applicants respectfully submit that the rejection of claims 1, 5-7, 19, 22, and 23 under 35 U.S.C. § 112, first paragraph, for alleged lack of enablement has been overcome. Therefore, Applicants request the withdrawal of this rejection.

CONCLUSION

Applicants respectfully submit that the rejections under 35 U.S.C. §§ 103 and 112 have been overcome by the above remarks. Early allowance of pending claims 1, 5-7, and 19-23 is respectfully requested. Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "**Version**

with markings to show changes made". In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, Applicant petitions for any required relief including extensions of time and authorizes the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. 432722002621.

Respectfully submitted,

Dated: November 18, 2002 By: _____

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Specification:

At page 1, lines 1-2, please amend the title as follows:

INHIBITORS OF PROTEASOMAL ACTIVITY FOR STIMULATING BONE [AND HAIR] GROWTH.

At page 47, line 1, please amend the abstract as follows:

The present invention relates to c[C]ompounds that [inhibit the activity of NF-κB or]inhibit the activity of the proteasome or [both]the production of proteasomal proteins and promote bone formation [and hair growth]and are thus useful in treating osteoporosis, bone fracture or deficiency, primary or secondary hyperparathyroidism, periodontal disease or defect, metastatic bone disease, osteolytic bone disease, post-plastic surgery, post-prosthetic joint surgery, and post-dental implantation[; they also stimulate the production of hair follicles and are thus useful in stimulating hair growth, including hair density], in subject where this is desirable.

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EXHIBIT B

CHAPTER 61

AGENTS AFFECTING CALCIFICATION AND BONE TURNOVER

Calcium, Phosphate, Parathyroid Hormone, Vitamin D, Calcitonin, and Other Compounds

Robert Marcus

In previous editions, this chapter was focused on hormones involved with calcium homeostasis, mechanisms by which they act to maintain blood Ca^{2+} concentrations within normal limits, and the derangements in Ca^{2+} physiology associated with insufficiency or excess of these hormones. In recent years, there has been a shift in the relative importance of the prevalence and severity of these disorders. Primary hyperparathyroidism is more commonly diagnosed than in years past, but most commonly it appears today as a mild disorder that does not necessarily require treatment. By contrast, osteoporotic fracture, particularly of the hip, has emerged as a major public health problem and an important contributor to disability, mortality, and health care costs in industrialized countries. Considerable information has been obtained regarding the acquisition and subsequent loss of bone, as well as the contributions of genetics, diet, physical activity, and reproductive hormone status to skeletal health. Important, albeit incomplete knowledge has been obtained concerning the central role of bone remodeling as the final pathway of adult bone loss.

A rapidly increasing body of evidence supports the concept that regular physical activity, adequate Ca^{2+} intake, either through diet or supplements, and timely use of estrogen replacement therapy will decrease bone remodeling, constrain bone loss, and reduce fracture risk. However, treatment of established osteoporosis remains a formidable challenge. Like estrogen and Ca^{2+}, other recently developed therapies, such as calcitonin and bisphosphonates, act primarily by slowing bone resorption rather than by stimulating new bone formation. Although these agents are welcome additions, they will not solve the problem of restoring normal bone mass. In fact, since bone remodeling is a coupled process, agents that suppress bone resorption ultimately decrease bone formation. The primary challenge for future research in this field is to develop agents that safely increase bone mass. Fluoride remains a potential candidate, although it has a very narrow therapeutic window. Recent studies involving low doses permit optimism that fluoride may become a useful agent to achieve meaningful increases in bone mass and reduce fracture risk. At present, there is considerable interest in developing analogs of parathyroid hormone and vitamin D, traditional skeletal growth factors such as growth hormone and insulin-like growth factor I, and various bone morphogenetic proteins as potential therapies for osteoporosis.

Another recent development is the recognition that vitamin D may have an important role as a cellular differentiation factor in systems not directly related to calcium metabolism. Calcitriol, the hormonal form of vitamin D, shows considerable promise as a treatment for psoriasis and also is under study for several malignancies. Therapeutic utility of calcitriol is limited by its calcemic effects, but noncalcemic calcitriol analogs are under development. Such analogs may offer a new approach to manage patients with diverse conditions, ranging from primary and secondary hyperparathyroidism to cancer and leukemia.

long-term remodeling inefficiency, dietary inadequacy, and activation of the parathyroid axis with age. Compelling evidence has not been presented that these two entities are truly distinct, and the model fails to account for decreased bone mass resulting from inadequate skeletal acquisition during growth. Although many osteoporotic women undoubtedly have experienced excessive menopausal bone loss, it may be more appropriate to consider osteoporosis as the result of multiple physical, hormonal, and nutritional factors acting alone or in concert.

Skeletal Organization. Because bone turnover rates differ from one portion of the skeleton to the next, it is useful to consider the appendicular, or peripheral, skeleton separate from the axial, or central, skeleton. Appendicular bones make up 80% of whole body bone mass and are composed predominantly of compact cortical bone. Axial bones, such as the spine and pelvis, contain substantial amounts of trabecular bone within a thin cortex. Trabecular bone consists of highly connected bony plates that resemble honeycomb. The intertrabecular interstices contain bone marrow and fat. For several reasons, alterations in bone turnover are observed first and most extensively in axial bone rather than in the appendicular skeleton. These include the facts that bone remodeling takes place on bone surfaces, that there is a higher surface density in trabecular bone compared to cortical bone, and that marrow precursor cells that ultimately participate in bone turnover lie in close proximity to trabecular surfaces.

Bone Mass. Bone density and fracture risk in later years reflect the maximal bone mineral content at skeletal maturity (peak bone mass) and the subsequent rate of bone loss. Major increases in bone mass, accounting for about 60% of final adult levels, occur during adolescence, mainly during years of highest growth velocity. Bone acquisition is almost complete by age 17 years in girls and by 20 years in boys. Inheritance accounts for much of the variance in bone acquisition; other factors include circulating estrogen and androgens, physical activity, and dietary calcium.

Bone is lost during adult life. Radiographic measurements of metacarpal bone by Garn and colleagues (1966) described a characteristic trajectory of bone mass throughout life, by which bone mass levels off during the third decade, remains stable until age 50, and then progressively declines. Similar trajectories occur for men, women, and all ethnic groups. The fundmental accuracy of this model has been amply confirmed for cortical bone, although trabecular bone loss probably begins prior to age 50 at some sites. In women, loss of estrogen at menopause accelerates the rate of bone loss for several years.

The primary regulators of adult bone mass include physical activity, reproductive endocrine status, and calcium intake. Optimal maintenance of bone requires sufficiency in all three areas, and deficiency in one area is not compensated by excessive attention to another. For example, amenorrheic athletes lose bone despite frequent high-intensity exercise (Marcus *et al.*, 1985).

Prevention and Treatment of Osteoporosis

A rational strategy to prevent osteoporosis follows from the above considerations. Regular physical activity of reasonable intensity is endorsed at all ages. For children and adolescents, adequate dietary calcium is important if peak bone mass is to reach the level appropriate for genetic endowment. Attention to nutritional status may be required in the seventh decade and beyond, taking the form of increased dietary calcium or of calcium and/or vitamin D supplements. For women at menopause, timely administration of estrogen is the most powerful intervention to preserve bone and protect against fracture. Indeed, at any age, prevention or correction of hypogonadism is an important consideration. With appropriate lifelong attention to these preventive factors, important reductions in fracture risk can be achieved.

Pharmacological agents used to manage osteoporosis act by decreasing the rate of bone resorption, thereby slowing the rate of bone loss, or by promoting bone formation. The only drugs currently approved in the United States for use in osteoporosis are those that decrease resorption. Since bone remodeling is a coupled process, antiresorptive drugs ultimately decrease the rate of bone formation. Thus, antiresorptive therapy cannot lead to substantial gain in bone mass. Modest increases in bone mass that are typically seen during the first year of antiresorptive therapy represent a constriction of the remodeling space to a new steady-state level, after which bone mass reaches a plateau. One consequence of this phenomenon is that therapeutic trials in osteoporosis must be of sufficient duration to determine whether an increase in bone mass represents anything more than a simple reduction in remodeling space. It appears that at least 2 years are required for this purpose.

Antiresorptive Agents. ***Calcium.*** The physiological roles of Ca^{2+} and its use in the treatment of hypocalcemic disorders are discussed above. The rationale for using supplemental calcium to protect bone mass varies with time of life. For preteens and adolescents, adequate substrate calcium is required for bone accretion. Controlled trials indicate supplemental calcium promotes adolescent bone acquisition (Johnston *et al.*, 1992; Lloyd *et al.*, 1993), but its impact on peak bone mass is not known. Higher calcium intake during the third decade of life is positively related to the final phase of bone acquisition (Recker *et al.*, 1992). There is controversy about the role of calcium during the early years after menopause, when the primary stimulus for bone loss is estrogen withdrawal. Although no effect of